Please replace the paragraph beginning at page 14, line 26, with the following:

Figure 15D shows gel-shift assays of binding affinity. A three-fold dilution series of each protein was tested for binding to its DNA target (SEQ ID NOS:207, 144, 240 and 141, respectively), with the highest concentration in lane 10 and the lowest concentration in lane 2. Lane 1 contains probe alone. Apparent K_d's, derived from the average of 3 such studies, are indicated at right. For mVZ+426 and mVZ+509, K_d's are provided as upper bounds (<0.01 nM), since the use of 0.01 nM of probe has probably led to an underestimate of the affinity of these proteins.

Please replace the paragraph beginning at page 17, line 20, with the following:

The term "zinc finger protein" or "ZFP" refers to a protein having DNA binding domains that are stabilized by zinc. The individual DNA binding domains are typically referred to as "fingers" A ZFP has least one finger, typically two, three, four, five, six or more fingers. Each finger binds from two to four base pairs of DNA, typically three or four base pairs of DNA. A ZFP binds to a nucleic acid sequence called a target site or target segment. Each finger typically comprises an approximately 30 amino acid, zinc-chelating, DNA-binding subdomain. An exemplary motif characterizing one class of these proteins (C_2H_2 class) is -Cys-$(X)_{2-4}$-Cys-$(X)_{12}$-His-$(X)_{3-5}$-His (SEQ ID NO:208) (where X is any amino acid). Additional classes of zinc finger proteins are known and are useful in the practice of the methods, and in the manufacture and use of the compositions disclosed herein (see, e.g., Rhodes et al. (1993) Scientific American 268:56-65). Studies have demonstrated that a single zinc finger of this class consists of an alpha helix containing the two invariant histidine residues coordinated with zinc along with the two cysteine residues of a single beta turn (*see, e.g.*, Berg & Shi, *Science* 271:1081-1085 (1996)).

Please replace the paragraph beginning at page 34, line 3, with the following:

The zinc finger proteins (ZFPs) disclosed herein are proteins that can bind to DNA in a sequence-specific manner. As indicated supra, these ZFPs can be used in a

variety of applications, including modulating angiogenesis and in treatments for ischemia. An exemplary motif characterizing one class of these proteins, the C_2H_2 class, is -Cys-$(X)_{2-4}$-Cys-$(X)_{12}$-His-$(X)_{3-5}$-His (SEQ ID NO:208) (where X is any amino acid). Several structural studies have demonstrated that the finger domain contains an alpha helix containing the two invariant histidine residues and two invariant cysteine residues in a beta turn coordinated through zinc. However, the ZFPs provided herein are not limited to this particular class. Additional classes of zinc finger proteins are known and can also be used in the methods and compositions disclosed herein (see, e.g., Rhodes, et al. (1993) Scientific American 268:56-65). In certain ZFPs, a single finger domain is about 30 amino acids in length. Zinc finger domains are involved not only in DNA-recognition, but also in RNA binding and in protein-protein binding.

Please replace the paragraph beginning at page 36, line 3, with the following:

Tables 3 and 4 show the amino acid sequences of a number of different ZFPs and the corresponding target sites to which they bind. Table 3 lists ZFPs that bind to target sites that include 9 nucleotides. The first column in this table lists an internal reference name of the ZFP. Column 2 includes the 9 base target site bound by a three-finger zinc finger protein, with the target sites listed in 5' to 3' orientation. The corresponding SEQ ID NO: for the target site is listed in column 3 (SEQ ID NOS:1-29 and 244). The amino acid sequences of portions of the three zinc finger components involved in recognition are listed in columns 4, 6 and 8, and their corresponding SEQ ID NOS: are listed in columns 5 (SEQ ID NOS:30-58) , 7 (SEQ ID NOS:59-87, 112, and 245-252) and 9 (SEQ ID NOS:42, 64, and88-116), respectively. The numbering convention for zinc fingers is defined below. Column 10 lists the dissociation constants for some of the ZFP/target site complexes. Methods for determining such constants are described *infra*. Excluding cross-strand interactions, each finger binds to a triplet of bases (a target subsite) within a corresponding target sequence. The first finger binds to the first triplet starting from the 3' end of a target site, the second finger binds to the second triplet, and the third finger binds the third (i.e., the 5'-most) triplet of the target sequence. Thus, for example, the RSDHLAR finger (SEQ ID NO:30) of the ZFP BVO 13A (first column of Table 3)

binds to 5'GGG3', the DRSNLTR finger (SEQ ID NO:59) binds to 5'GAC3' and the RSDALTQ finger (SEQ ID NO:88) binds to 5'ATG3'.

Please replace the paragraph beginning at page 36, line 20, with the following:

Table 4 provides information on six-finger ZFPs targeting VEGF genes. Table 4 has a similar format to Table 3, with column 1 indicating the internal reference name of the ZFP. In contrast to Table 3, however, column 2 of Table 4 includes the 18 base target site recognized by a six-finger protein (here, too, targets are listed in a 5' to 3' orientation), with the corresponding SEQ ID NO: listed in column 3 (SEQ ID NOS:117-119). The amino acid sequences of portions of the six zinc finger components involved in recognition are listed in columns 4, 6, 8, 10, 12 and 14, with associated SEQ ID NOS: being listed in columns 5 (SEQ ID NOS:120-122), 7 (SEQ ID NOS:123-125), 9 (SEQ ID NOS:126-128), 11 (SEQ ID NOS:129-131), 13 (SEQ ID NOS:132-134) and 15 (SEQ ID NOS:135-17), respectively. In ZFPs of this type, the first finger binds to the first triplet starting from the 3' end of a target site, the second finger binds to the second triplet, the third finger binds the third triplet, the fourth finger binds to the fourth triplet, the fifth finger binds to the fifth triplet and the sixth finger binds to the sixth (i.e., the 5'-most) triplet of the target sequence (again excluding cross-strand interactions). Hence, for the ZFP named BVO 10A-9A, the first finger QSSDLRR (SEQ ID NO:120) binds 5'GCT3', the second finger RSDHLTR (SEQ ID NO:123) binds 5'GGG3', the third finger DRSALAR (SEQ ID NO:126) binds 5'GTC3', the fourth finger RSDHLAR (SEQ ID NO:129) binds 5'GGG3', the fifth finger RSDNLAR (SEQ ID NO:132) binds 5'GAG3' and the sixth finger RSDALTR (SEQ ID NO:135) binds 5'GTG3'.

Please replace the paragraph beginning at page 38, line 26, with the following:

The relative order of fingers in a zinc finger protein from N-terminal to C-terminal determines the relative order of triplets in the 3' to 5' direction in the target. For example, if a zinc finger protein comprises from N-terminal to C-terminal first, second and third fingers that individually bind, respectively, to triplets 5' GAC3', 5'GTA3' and

5"GGC3' then the zinc finger protein binds to the target segment 3'CAGATGCGG5' (SEQ ID NO:209). If the zinc finger protein comprises the fingers in another order, for example, second finger, first finger, third finger, then the zinc finger protein binds to a target segment comprising a different permutation of triplets, in this example, 3'ATGCAGCGG5' (SEQ ID NO:210). See Berg & Shi, *Science* 271, 1081-1086 (1996). The assessment of binding properties of a zinc finger protein as the aggregate of its component fingers may, in some cases, be influenced by context-dependent interactions of multiple fingers binding in the same protein.

Please replace the paragraph beginning at page 39, line 16, with the following:

Linkage can be accomplished using any of the following peptide linkers. T G E K P (SEQ ID NO:211), (Liu et al., 1997, supra.); $(G_4S)n$ (SEQ ID NO:212), (Kim et al., Proc. Natl. Acad. Sci. U.S.A. 93: 1156-1160 (1996.); GGRRGGGS (SEQ ID NO:213); LRQRDGERP (SEQ ID NO:214); LRQKDGGGSERP (SEQ ID NO:215); $LRQKD(G_3S)_2ERP$ (SEQ ID NO:216). Alternatively, flexible linkers can be rationally designed using computer programs capable of modeling both DNA-binding sites and the peptides themselves or by phage display methods. In a further variation, noncovalent linkage can be achieved by fusing two zinc finger proteins with domains promoting heterodimer formation of the two zinc finger proteins. For example, one zinc finger protein can be fused with fos and the other with jun (see Barbas et al., WO 95/119431).

Please replace the paragraph beginning at page 39, line 31, with the following:

A component finger of zinc finger protein typically contains about 30 amino acids and, in one embodiment, has the following motif (N-C) (SEQ ID NO:208):

$$\text{Cys-}(X)_{2\text{-}4}\text{-Cys-X.X.X.X.X.X.X.X.X.X.X-His-}(X)_{3\text{-}5}\text{-His}$$

$$\text{-1 1 2 3 4 5 6 7}$$

Please replace the paragraph beginning at page 40, line 14, with the following:

Please replace the paragraph beginning at page 74, line 22, with the following:

Construction of Zinc Finger Fusion Proteins. VEGF-A-targeted zinc fingers were assembled in an SP1 backbone and cloned into the pcDNA3 mammalian expression vector (Invitrogen, Carlsbad, CA) as described previously (Zhang et al., supra; WO 00/41566; and WO 00/42219). A CMV promoter was used to drive the expression of all the ZFPs in mammalian cells. All ZFP constructs contained an N-terminal nuclear localization signal (Pro-Lys-Lys-Lys-Arg-Lys-Val; SEQ ID NO:224) from SV40 large T antigen, a Zinc Finger DNA-binding domain, an activation domain, and a FLAG peptide (Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys; SEQ ID NO:225). ZFP-VP16 fusions contained the herpes simplex virus VP16 activation domain from amino acid 413 to 490 (Sadowski et al., supra; Zhang et al, supra; WO 00/41566; and WO 00/42219). ZFP-p65 fusions contained the human NF-κB transcription factor p65 subunit (amino acid 288-548) as the activation domain (Ruben et al., supra).

Please replace the paragraph (TABLE 5) beginning at page 74, line 22, with the following:

TABLE 5: NUCLEOTIDE SEQUENCES OF PRIMERS AND PROBES USED FOR TAQMAN ANALYSIS

	Sequence	SEQ ID NO:
VEGF-A forward primer	5'-GTGCATTGGAGCCTTGCCTTG-3'	226
VEGF-A reverse primer	5'-ACTCGATCTCATCAGGGTACTC-3'	227
VEGF-A Taqman Probe	5'-FAM-CAGTAGCTGCGCTGATAGACATCCA-TAMRA-3'	228
GAPDH forward primer	5'-CCATGTTCGTCATGGGTGTGA-3'	229
GAPDH reverse primer	5'-CATGGACTGTGGTCATGAGT-3'	230
GAPDH Taqman Probe	5'-FAM-TCCTGCACCACCAACTGCTTAGCA-TAMRA-3'	231
VP16-FLAG forward primer	5'-CATGACGATTTCGATCTGGA-3'	232
VP16-FLAG reverse primer	5'-CTACTTGTCATCGTCGTCCTTG-3'	233
VP16-FLAG Taqman Probe	5'-FAM-ATCGGTAAACATCTGCTCAAACTCGA-TAMRA-3'	234

Abbreviations: FAM: aminofluorescein; TAMRA: tetramethylrhodamine

Please replace the paragraph beginning at page 78, line 1, with the following:

yielding constructs pMal-c2 '1-3' and pMal-c2 '4-6'. Next, these two genes were joined via a short DNA spacer encoding a flexible peptide linker. This was accomplished as follows: (i) PCR of the '4-6' ZFP gene using the primers 5' CCCAGATCTGGTGATGGCAAGAAGAAGCAGCACCATCTGCCACATCCAG (SEQ ID NO:241) and 5' CCCAAGCTTAGGATCCACCCTTCTTGTTCTGGTGGGT (SEQ ID NO:242); (ii) digestion of the resultant fragment with Bgl II and Hind III (sites underlined in primers); and (iii) ligation into the BamHI and Hind III sites of the pMal-c2 '1-3'. The resultant protein, VZ+57, consists of the '1-3' and '4-6' three-finger modules connected by a flexible peptide linker, with the amino acid sequence between the second zinc-coordinating histidine of finger 3 and the first zinc-coordinating cysteine of finger 4 (both underlined) as follows: HQNKKGGSGDGKKKQHIC (SEQ ID NO:243).

Please replace the paragraph beginning at page 90, line 15, with the following:

Construction of retroviral vectors. The retroviral vectors described here are derived from a pLXSN, a Moloney murine leukemia virus-based vector containing a neomycin resistance gene under the control of an internal simian virus (SV40) promoter. Using EcoR1 and Xho1 restriction sites, the zinc finger expression cassette was placed immediately downstream of the LTR in pLXSN. Briefly, all ZFP constructs contained an N-terminal nuclear localization signal (Pro-Lys-Lys-Lys-Arg-Lys-Val; SEQ ID NO:224) from SV40 largeT antigen, a Zinc Finger DNA-binding domain, the herpes simplex virus VP16 activation domain from amino acid 413 to 490, and a FLAG peptide (Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys; SEQ ID NO:224). The LXSN vectors were produced in the 293 AMPHO-PAK™ cell line and had titers ranging from 0.5-1.0 x 10^6 G418-resistant colony-forming units. Virus-containing supernatant was collected 48 hr after transfection, filtered through 0.45-mm-pore-size filter and used fresh for transduction of target cells or aliquoted and stored at –80 °C.

Please replace the paragraph (**TABLE 3**) beginning at page 104, line 1, with the following amended table:

PATENT

TABLE 3 Target sites and recognition helix sequences of human VEGF-targeted ZFPs

ZFP NAME	TARGET	SEQ. ID NO	F 1	SEQ ID NO	F 2	SEQ ID NO	F 3	SEQ ID NO	K_d (nM)
BVO 13A	ATGGACGGG	1	RSDHLAR	30	DRSNLTR	59	RSDALTQ	88	<.02
EP10A	KGGGGCTGG	2	RSDHLTT	31	DRSHLAR	60	RSDHLSK	89	0.35
GATA82Z678	GAGKGKGYG	3	RLDSLLR	32	DRDHLTR	61	RSDNLAR	90	1.8
HBV 3	GGGGGAGGW	4	QTGHLRR	33	QSGHLQR	62	RSDHLSR	91	30
HP38 4A	GGDTGGGGG	5	RSDHLAR	34	RSDHLTT	63	QRAHLAR	92	0.75
HUM 17A	ARGGGGGAG	6	RSDNLAR	35	RSDHLSR	64	RSDNLTQ	93	<.02
HUM 19A	TGGGCAGAC	7	DRSNLTR	36	QSGDLTR	65	RSDHLTT	94	0.02
MTS 5A	TGGGGGTGG	8	RSDHLTT	37	RSDHLTR	66	RSDHLTT	95	0.07
MX1E	ATGGACGGG	9	RSDHLAR	38	DRSNLTR	67	RSDALSA	96	3.4
PDF 5A	GYAGGGGCC	10	DRSSLTR	39	RSDHLSR	68	QSGSLTR	97	.23
RAT 24A	GDGGAAGHC	11	ERGTLAR	40	QSGNLAR	69	RSDALAR	98	<.02
SAN 16A	AKGGAAGGG	12	RSDHLAR	41	QSGNLAR	70	RSDALRQ	99	1.03
USX 3A	GCCGGGGAG	13	RSDNLTR	42	RSDHLTR	71	DRSDLTR	100	0.06
VEGF 1	GGGGAGGVK	14	TTSNLRR	43	RSSNLQR	72	RSDHLSR	101	2.83
VEGF 1*	GGGGAGGVK	15	TTSNLRR	44	RSSNLQR	73	RSDHLSR	102	3
VEGF 1A	GGGGAGGVK	16	TTSNLRR	45	RSDNLQR	74	RSDHLSR	103	0.2
VEGF 1B	GGGGAGGAT	17	QSSNLAR	46	RSDNLQR	75	RSDHLSR	104	2
VEGF 1C	GGGGVGGAT	18	TTSNLAR	47	RSDNLQR	76	RSDHLSR	105	1
VEGF 1D	GGGGAGGMT	19	QSSNLRR	48	RSDNLQR	77	RSDHLSR	106	2
VG 10Ai	GAWGGGGGC	20	DSGHLTR	49	RSDHLTR	78	QSGNLTR	107	ND
VG 1B	ATGGGGGTG	21	RSDALTR	50	RSDHLTR	79	RSDALTQ	108	ND
VG 4A	GGGGGCTGG	22	RSDHLTT	51	DRSHLAR	80	RSDHLSR	109	ND
VG 8A	GDGTGGGGN	23	QSSHLAR	52	RSDHLTT	81	RSDALAR	110	.35
VOP 28A-2	GGGGGCGCT	24	QSSDLRR	53	DRSHLAR	82	RSDHLSR	111	<.02
VOP 30A-4	GCTGGGGGC	25	DRSHLTR	54	RSDHLTR	83	QSSDLTR	112	<.02
ZFP NAME	TARGET	SEQ. ID NO	F 1	SEQ ID NO	F 2	SEQ ID NO	F 3	SEQ ID NO	K_d (nM)
VOP 32A-6	GGGGGTGAC	26	DRSNLTR	55	MSHHLSR	84	RSDHLSR	113	<.02
VOP 32B-7	GGGGGTGAC	27	DRSNLTR	56	TSGHLVR	85	RSDHLSR	114	<.02

VOP 35A-10	GCTGGAGCA	28	QSGSLTR	57	QSGHLQR	86	QSSDLTR	115	<.02
ZEN-7A 1	GGGGGHGCT	29	QSSDLRR	58	QSSHLAR	87	RSDHLSR	116	.63
VOP 29A-3	GAGGCTTGG	244	RSDHLTT	51	QSSDLTR	112	RSDNLTR	42	<.02
VOP 32-C	GGGGGTGAC	26	DRSNLTR	31	TSGHLTR	245	RSDHLSR	68	ND
VOP 32-D	GGGGGTGAC	26	DRSNLTR	36	TSGHLIR	246	RSDHLSR	68	ND
VOP 32-E	GGGGGTGAC	26	DRSNLTR	36	TSGHLSR	247	RSDHLSR	68	ND
VOP 32-F	GGGGGTGAC	26	DRSNLTR	36	TSGHLAR	248	RSDHLSR	68	ND
VOP 32-G	GGGGGTGAC	26	DRSNLTR	36	TSGHLRR	249	RSDHLSR	68	ND
VOP 32-H	GGGGGTGAC	26	DRSNLTR	36	TAGHLVR	250	RSDHLSR	68	ND
VOP 32-I	GGGGGTGAC	26	DRSNLTR	36	TTGHLVR	251	RSDHLSR	68	ND
VOP 32-J	GGGGGTGAC	26	DRSNLTR	36	TKDHLVR	252	RSDHLSR	68	ND

Please replace the paragraph (**TABLE 7**) beginning at page 107, line 1, with the following:

TABLE 7 Target sites and recognition helix sequences of rat VEGF-targeted ZFPs

ZFP NAME	TARGET	LOCATION	RECOGNITION HELICES
BV0 12A- 11A	GGAGAGGGGGCCGCAGTG (SEQ ID NO:182)	+785	F1: RSDALTR (SEQ ID NO:186) F2: QSGDLTR (SEQ ID NO:187) F3: ERGDLTR (SEQ ID NO:188) F4: RSDHLAR (SEQ ID NO:189) F5: RSDNLAR (SEQ ID NO:190) F6: QSSHLAR (SEQ ID NO:191)
BVO 14A- 13B	ATGGACGGGtGAGGCGGCG (SEQ ID NO:183)	+830	F1: RSDELTR (SEQ ID NO:192) F2: RSDELQR (SEQ ID NO:193) F3: RSDNLAR (SEQ ID NO:194) F4: RSDHLAR (SEQ ID NO:195) F5: DRSNLTR (SEQ ID NO:196) F6: RSDALTQ (SEQ ID NO:197)
VOP 32A	GGGGGTGAC (SEQ ID NO:184)	+420	F1: DRSNLTR (SEQ ID NO:198) F2: MSHHLSR (SEQ ID NO:199) F3: RSDHLSR (SEQ ID NO:200)
VOP 30A	GCTGGGGGC (SEQ ID NO:185)	+40 +514	F1: DRSHLTR (SEQ ID NO:201) F2: RSDHLTR (SEQ ID NO:202) F3: QSSDLTR (SEQ ID NO:203)
VOP 32B	GGGGGTGAC (SEQ ID NO:26)	+420	F1: DRSNLTR (SEQ ID NO:36) F2: TSGHLVR (SEQ ID NO:168) F3: RSDHLSR (SEQ ID NO:64)

Please insert the accompanying paper copy of the Sequence Listing, page numbers 1 to 51, at the end of the application.

REMARKS

Applicants request entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a floppy disk containing the above